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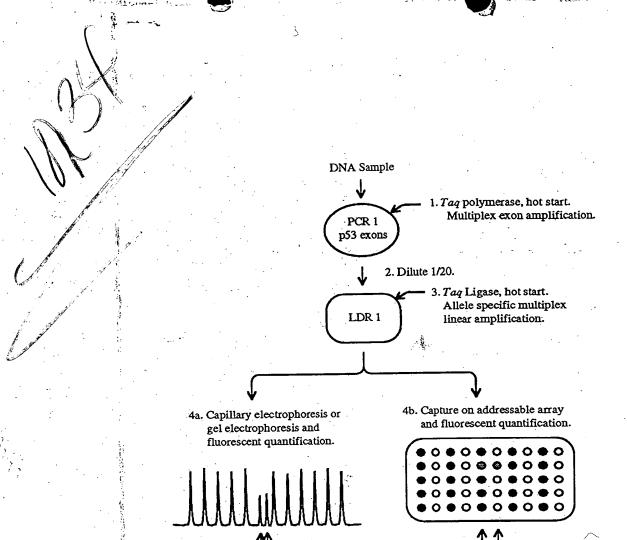
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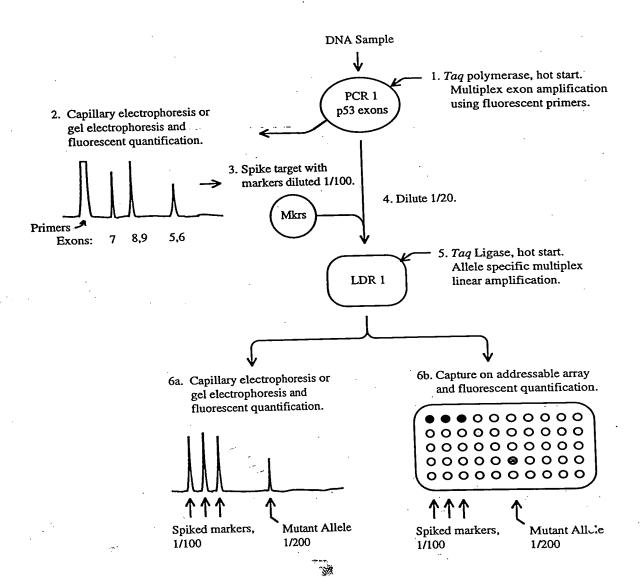


Normal Allele

Mutant Allele

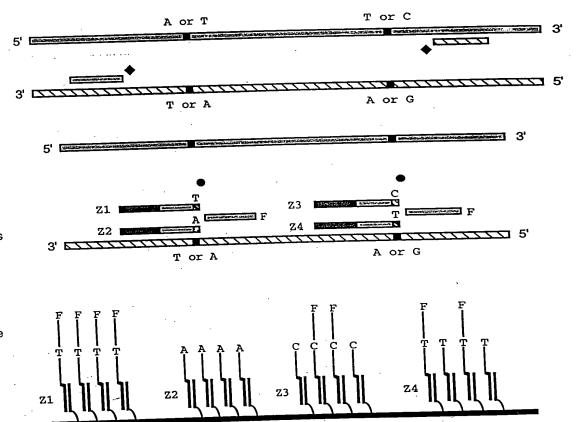
Normal Allele

Mutant Allele



PCR/LDR

- PCR amplify region(s)
 containing mutations
 using primers, dNTPs
 and Taq polymerase.◆
- 2. Perform LDR using allele-specific LDR primers and thermostable ligase. Allele specific oligonucleotides ligate to common oligonucleotides only when there is perfect complementarity at the junction.
- Capture fluorescent products on addressable array and quantify each allele.



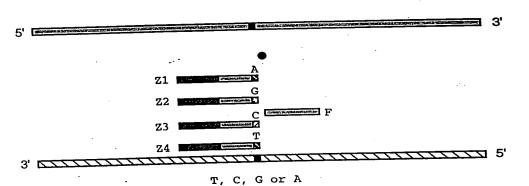
Homozygous: T allele only.

Heterozygous: C and T alleles.

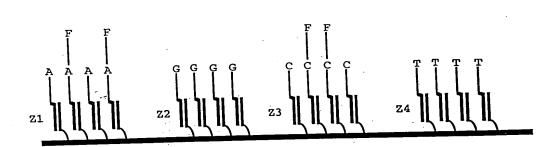
PCR/LDR

- PCR amplify region(s) containing mutations using primers, dNTPs and Taq polymerase.◆
- A, G, C or T

 Stranger transfer and a second control of the second
- 2. Perform LDR using allele-specific LDR primers and thermostable ligase. Allele specific oligonucleotides ligate to common oligonucleotides only when there is perfect complementarity at the junction.



3. Capture fluorescent products on addressable array and quantify each allele.

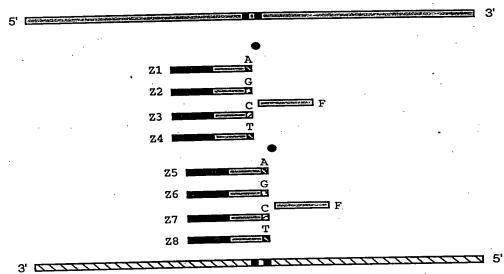


Heterozygous: A and C alleles.

PCR/ LDR: Nearby alleles

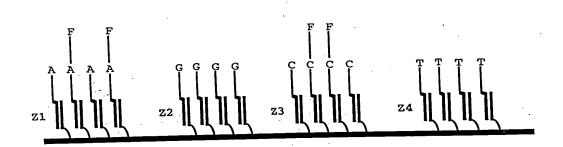
- PCR amplify region(s) containing mutations using primers, dNTPs and Taq polymerase. ◆
- A, G, C or T

 5' Manufactural and a second a
- 2. Perform LDR using allele-specific LDR primers and thermostable ligase. Allele specific oligonucleotides ligate to common oligonucleotides only when there is perfect complementarity at the junction.

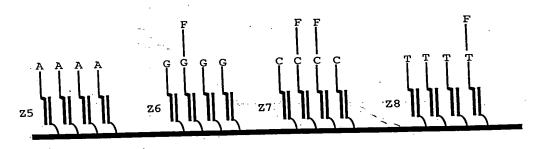


T, C, G or A

 Capture fluorescent products on addressable array and quantify each allele.



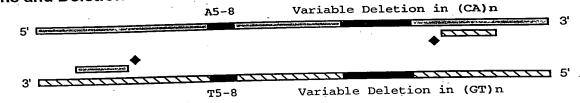
Heterozygous: A and C alleles.



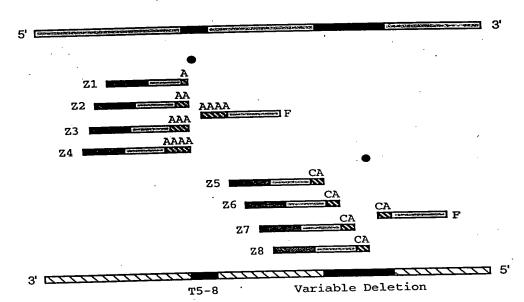
Heterozygous: G,C, and T alleles.

PCR/LDR: Insertions and Deletions

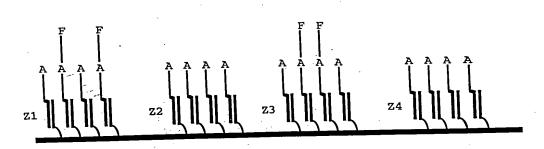
 PCR amplify region(s) containing mutations using primers, dNTPs and Taq polymerase.



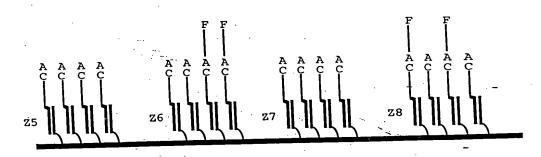
2. Perform LDR using allele-specific LDR primers and thermostable ligase. ■ Allele specific oligonucleotides ligate to common oligonucleotides only when there is perfect complementarity at the junction.



3. Capture fluorescent products on addressable array and quantify each allele.



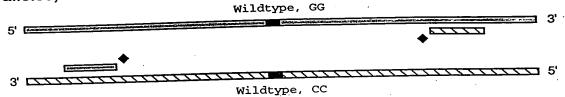
Heterozygous: A5 and A7 alleles.



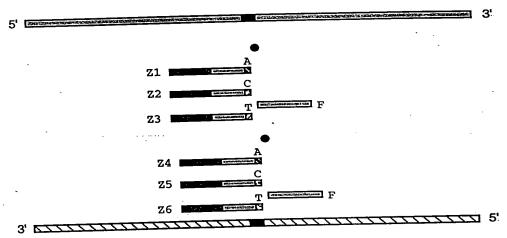
Heterozygous: (CA)5 and (CA)3 alleles.

PCR/ LDR: Adjacent alleles, cancer detection

 PCR amplify region(s) containing mutations using primers, dNTPs and Taq polymerase.◆

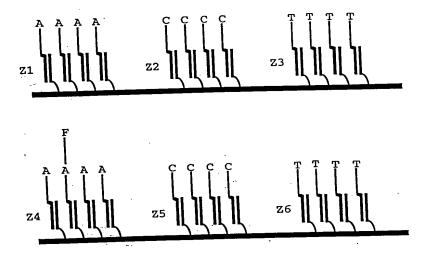


2. Perform LDR using allele-specific LDR primers and thermostable ligase. ● Allele specific oligonucleotides ligate to common oligonucleotides only when there is perfect complementarity at the junction.



Wildtype, CC

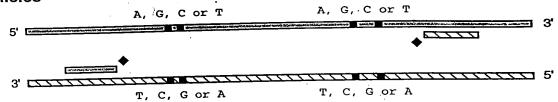
 Capture fluorescent products on addressable array and quantify each allele.



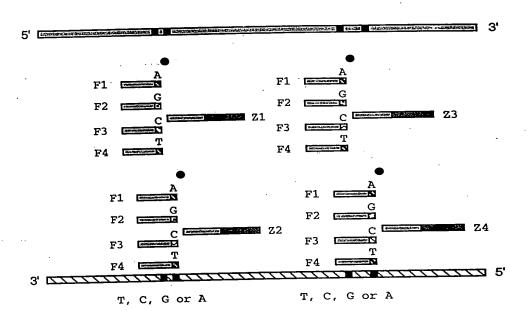
Gly to Asp mutation

PCR/ LDR: Nearby alleles

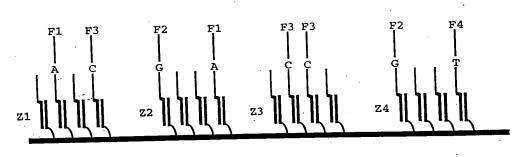
 PCR amplify region(s) containing mutations using primers, dNTPs and Taq polymerase.◆



2. Perform LDR using allele-specific LDR primers and thermostable ligase. ● Allele specific oligonucleotides ligate to common oligonucleotides only when there is perfect complementarity at the junction.



 Capture fluorescent products on addressable array and quantify each allele.



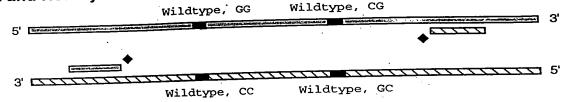
Heterozygous: ... A and C alleles.

Heterozygous: A and G alleles.

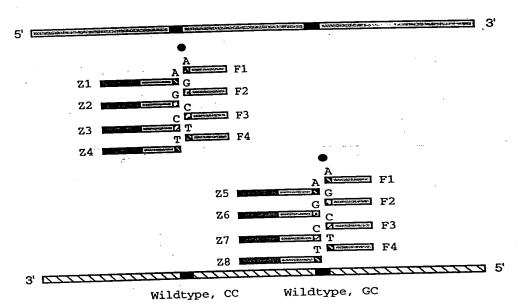
Homozygous: C allele. Heterozygous: G and T alleles.

PCR/ LDR: Adjacent and Nearby alleles

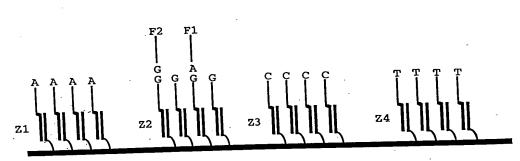
PCR amplify region(s)
containing mutations
using primers, dNTPs
and Taq polymerase.◆



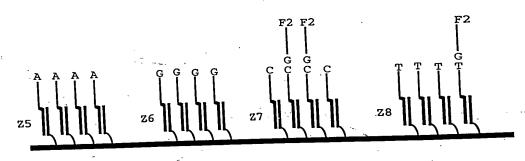
2. Perform LDR using allele-specific LDR primers and thermostable ligase. ● Allele specific oligonucleotides ligate to common oligonucleotides only when there is perfect complementarity at the junction.



 Capture fluorescent products on addressable array and quantify each allele.



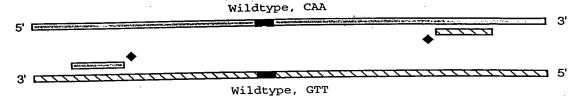
Heterozygous: Gly and Glu alleles.



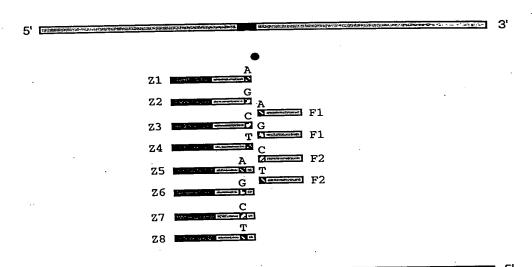
Heterozygous: Arg and Trp alleles.

PCR/ LDR: All alleles of a single codon

 PCR amplify region(s) containing mutations using primers, dNTPs and Taq polymerase.

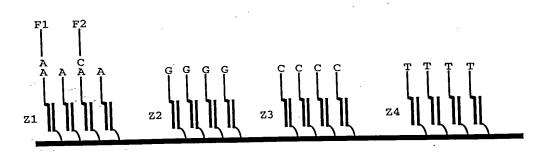


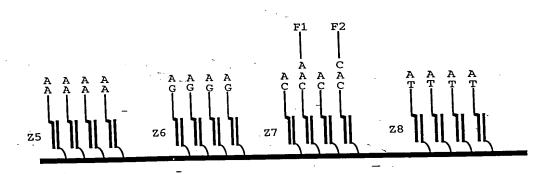
2. Perform LDR using allele-specific LDR primers and thermostable ligase. ● Allele specific oligonucleotides ligate to common oligonucleotides only when there is perfect complementarity at the junction.



Wildtype, GTT

 Capture fluorescent products on addressable array and quantify each allele.





Heterozygous: Gln and His alleles.

```
X
X^*
Y-PEG

X,Y = -OH
-CO_2H
-NH_2
Y-PEG

X^*,Y^* = -O(C=O)Z
-O(C=S)Z
-CO_2H
-(C=O)Z
-NH_2
-NH_2
-NH_2
-N=C=O
```

W = protecting group, e.g. Boc, Fmoc Z = activating group, e.g. imidazole (Im), p-nitrophenol (OPnp), hydroxysuccinimide (OSu), pentafluorophenol (OPfp) PEG = oligo or poly(ethylene glycol), backbone $(CH_2CH_2O)_n$ n = 6 to 200 (can also be grown by anionic polymerization with O) WSC = water soluble carbodiimide

Functional group transformations/activation (as needed), $X \to X^*, Y \to Y^*$

$$\begin{array}{lll} -\mathrm{OH} & \longrightarrow -\mathrm{O(CH_2)_nCO_2H} & n=1,2 \\ -\mathrm{OH} & \longrightarrow -\mathrm{O(C=O)NHCH_2CO_2H} \\ -\mathrm{OH} & \longrightarrow -\mathrm{O(C=O)CH_2NH_2} \\ -\mathrm{OH} & \longrightarrow -\mathrm{O(C=O)Im} \\ -\mathrm{OH} & \longrightarrow -\mathrm{O(C=S)SCH_2(C=O)NH_2} \\ -\mathrm{CO}_2 & \longrightarrow -(\mathrm{C=O)NH(CH_2)_nNH_2} & n=2,6 \\ -\mathrm{CO}_2 & \longrightarrow -(\mathrm{C=O})Z \\ -\mathrm{NH}_2 & \longrightarrow -\mathrm{NH(C=O)(CH_2)_nCO_2H} & n=2,3 \end{array}$$

Covalent linkage, X* + Y*

(B) Ac-Cys-Probe + N-(CH₂)_nC-Support

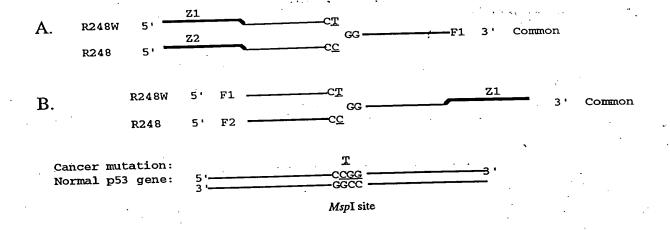
O
$$n = 1, 2, \text{ or } 5$$
 $pH 8$

CH₃C-N-CH-C-Probe

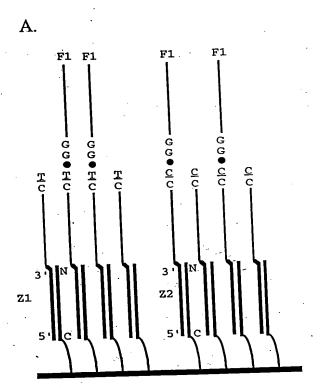
H

CH₂

N-(CH₂)_nC-Support



B.



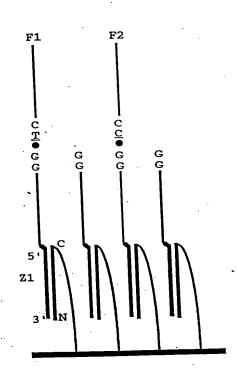
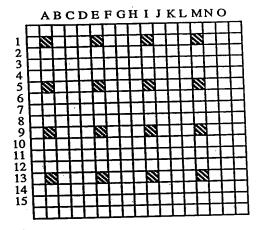
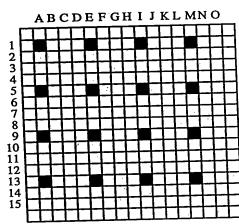


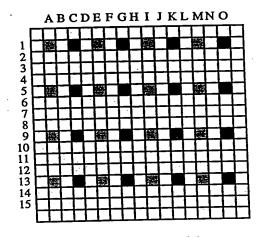
FIGURE 13

A

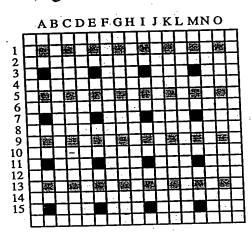


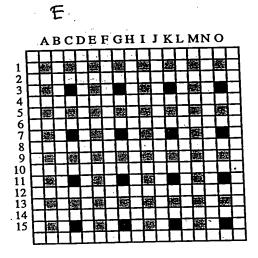
B

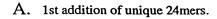




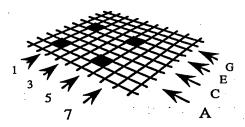
D

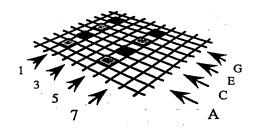






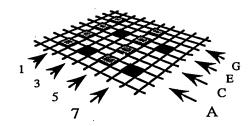


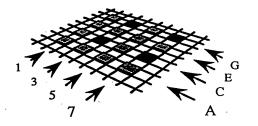




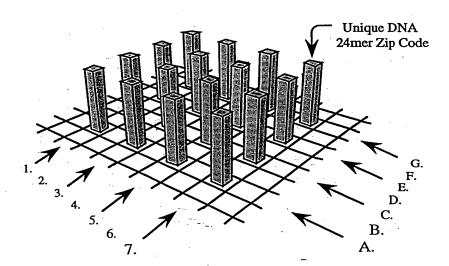
C. 3rd addition of unique 24mers.

D. 4th addition of unique 24mers.









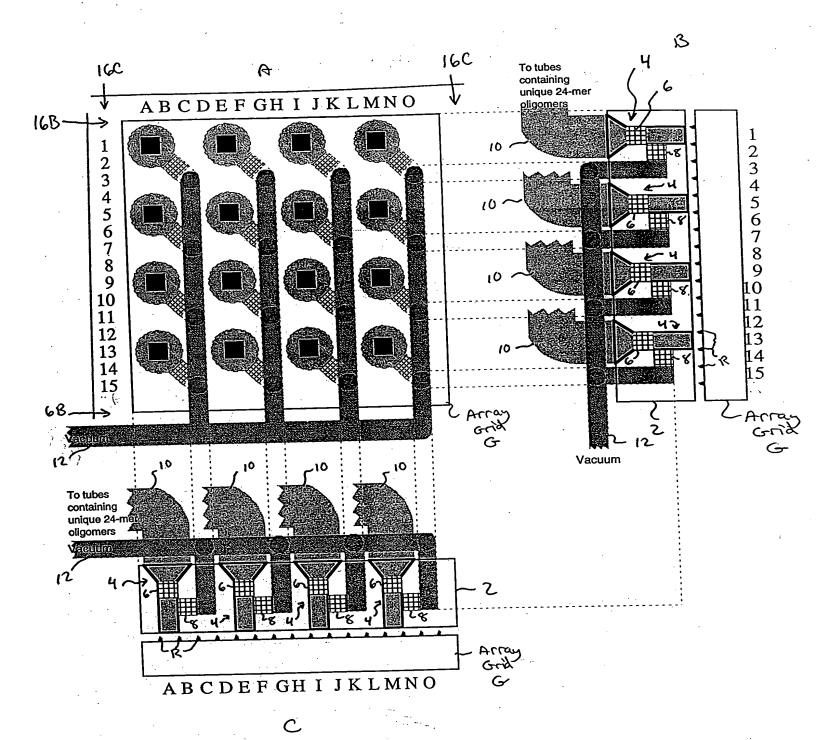


FIGURE 16

3

	2nd two bases)												•			
1st tv	wo 🗸	TT	TC	TG	TA	СТ	CC	CG	CA	GT	GC	GG	GA	AT	AC		AA
base	TT							16'			23'		TTGA 6			TAG 8	
	тс			TCTC 1		30'	TCCC 3			TCGT 5							6
	TG		TGTC 2		36'			TGCG 4						TGAT 7		11'	
	TA	· -					18'		TACA 36			33'					
	СТ	32'		CTTO 9	3				CTCA 11	CTGT 13							8']
	CC				CCT/ 33	1				29'				CCAT 15			
	CG	CGT1	T	12'					4'					28'			CGAA 16
	CA		34'			25'		CACC 12			CAGC 14		1'			9'	
	GT					GTC 19					GTGC 22			31'			
	GC	GCT 17	Т	14											22'		GCAA 23
	GG		20)'	GG [*]								3'		GGAC . 24		
	GA			GA 3			GAC 20	c	2'	GAG 21							
	AT							ATC 28				<u>[15'</u>	200000000000000000000000000000000000000		ATA(
	AC	755000000	2	1'		AC 2	CT 7					ACG 29				13'	
	AC	}		AC	5TG 25		AGC 35	CC		27	"		AGC 30		19'	YUU	
	A.		AA 2	TC 26				10)'		17					AAA 32	G





F

1st Tetramer addition (columns)

								_		
I	1	ſ	2		3	I	4		5	
۱	1	۱	2	١	3		4	۱	5	
۱	1		2	۱	3		4	I	5	
	1		2		3	l	4	١	5	
	1		2	١	3	١	4	١	5	١

B
2nd Tetramer addition

(rows)

6	6	6	6	6
5	5	5	5	5
4	4	4	4	4
3	3	3	3	3
2	2	2	2	2

3rd Tetramer addition (columns)

	_				,			,
3		4	۱	5		6	١	1
3	١	4	l	5		6		1
3		4		5		6		1
3		4	ľ	5		6		1
3		4	١	5	١	6	١	1
\mathbf{L}	4		4	_		Ъ	-	_

4th Tetramer addition (rows)

 \mathcal{D} .

2	2	2	2	2]
1	1	1	1	1]
6	6	6	6	6	
5	5	5	5	5	
4	4	4	4	4	

5th Tetramer addition (columns)

_					,	_				
ヒ	6		1		2		3		4	
	6		1	١	2	۱	3		4	
	6	۱	1		2	I	3	H	4	
	6		1		2	ľ	3		4	
	6		1		2		3		4	

6th Tetramer addition (rows)

				_
3	3	3	3	
2	2.	2	2]
.1	1,	1	1	
6	6	6	6	
5	5	5	5	
	3 2 1 6	2 2.	2 2 2	2 2 2 2 1 1 1 1 1

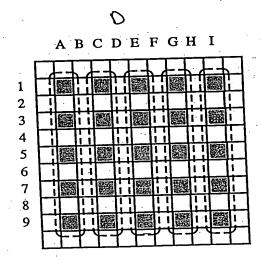
Addressable array with full length PNA 24mers

Add	iressable all	ay willi luli h	ongui I I i i i		
	1-6-3-2-6-3	2-6-4-2-1-3	3-6-5-2-2-3	4-6-6-2-3-3	5-6-1-2-4-3
<u> </u>					
	1-5-3-1-6-2	2-5-4-1-1-2	3-5-5-1-2-2	4-5-6-1-3-2	5-5-1-1-4-2
L					
	1-4-3-6-6-1	2-4-4-6-1-1	3-4-5-6-2-1	4-4-6-6-3-1	5-4-1-6-4-1
L					
	1-3-3-5-6-6	2-3-4-5-1-6	3-3-5-5-2-6	4-3-6-5-3-6	5-3-1-5-4-6
L_					
	1-2-3-4-6-5	2-2-4-4-1-5	3-2-5-4-2-5	5 . 4-2-6-4-3-5	5-2-1-4-4-5
L			·		



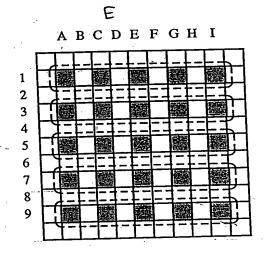
A B C D E F G H I

1
2
3
4
5
6
7
8
9



A B C D E F G H I

1
2
3
4
5
6
7
8
9



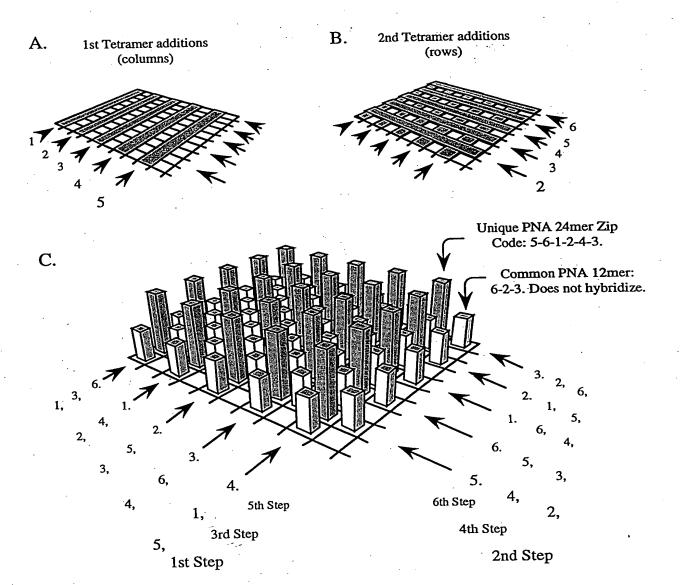


FIGURE 20

w minimini

- $B. \quad \ \ \, 1 \quad \ \, 1 \quad \,$

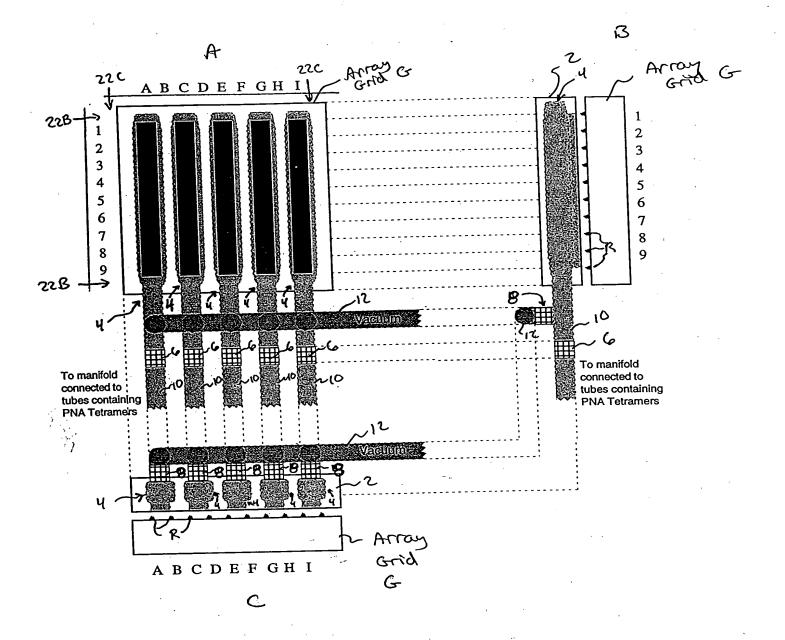


FIGURE 22

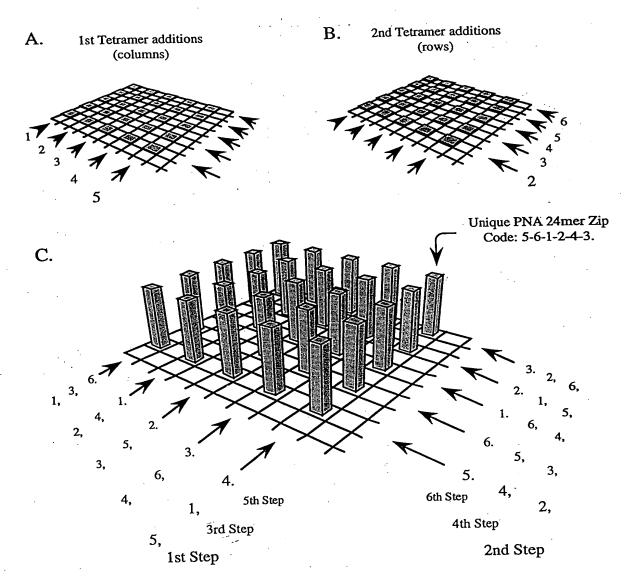


FIGURE 23

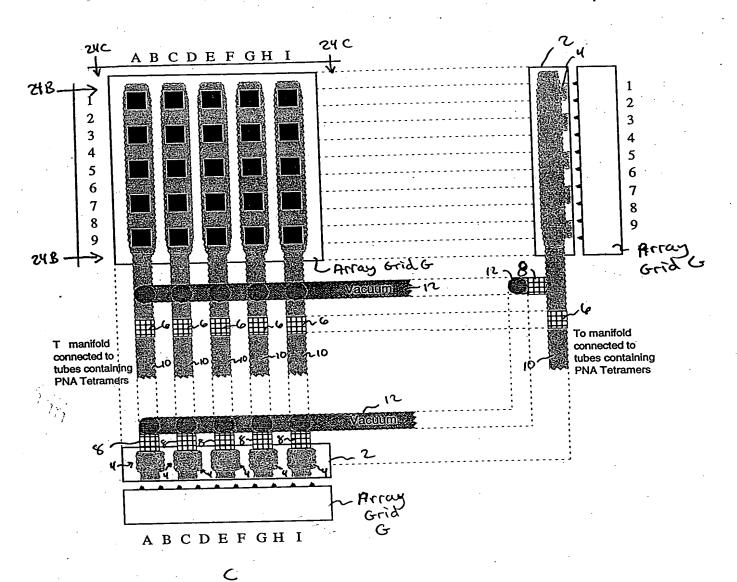
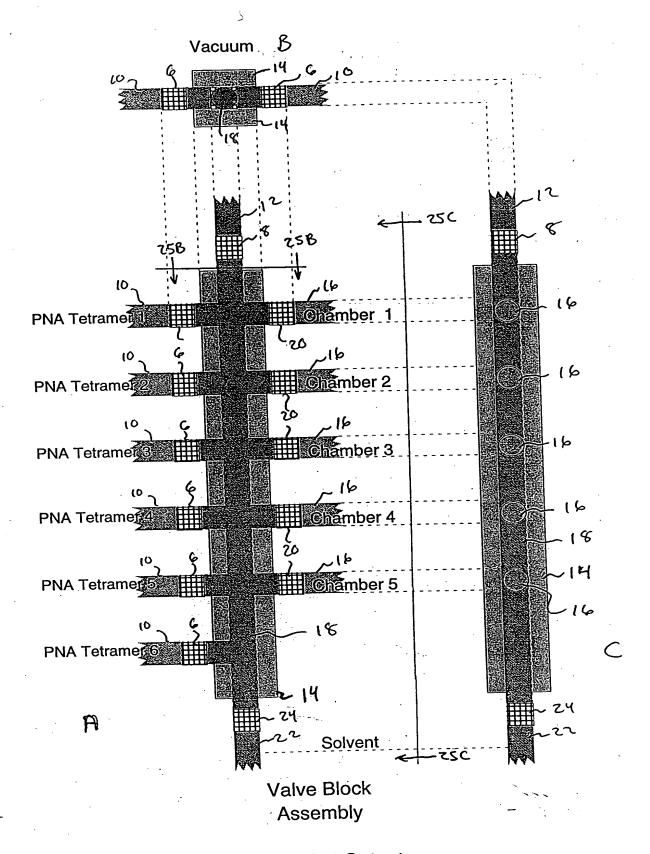


FIGURE 24



6 Inputs & 5 Outputs

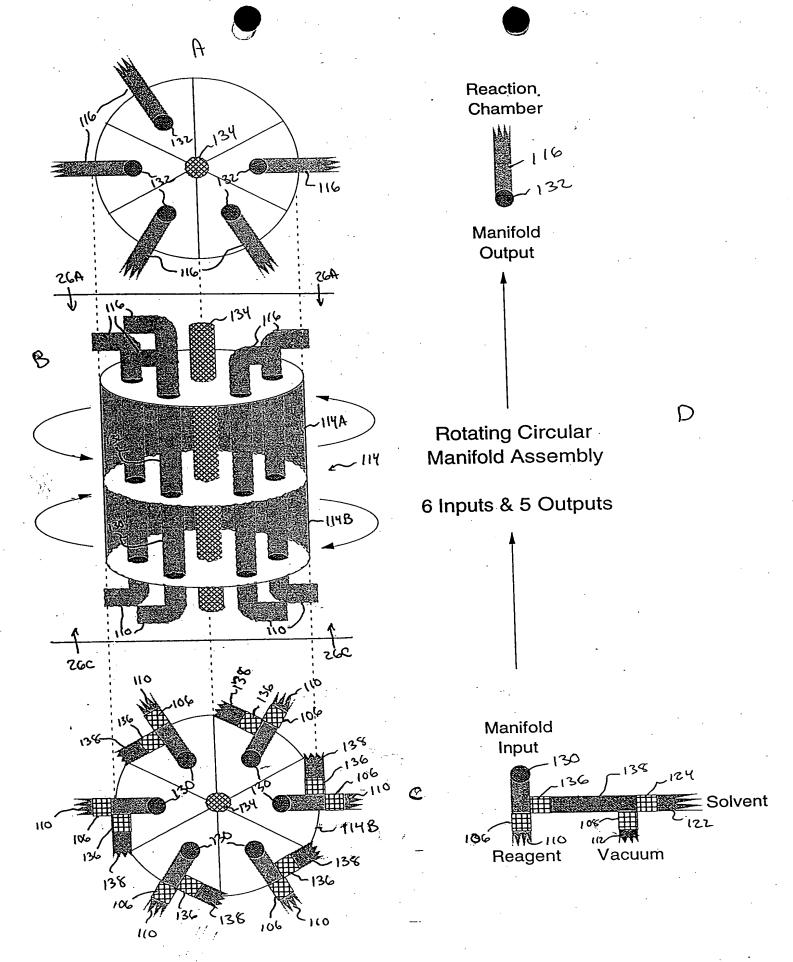


FIGURE 26

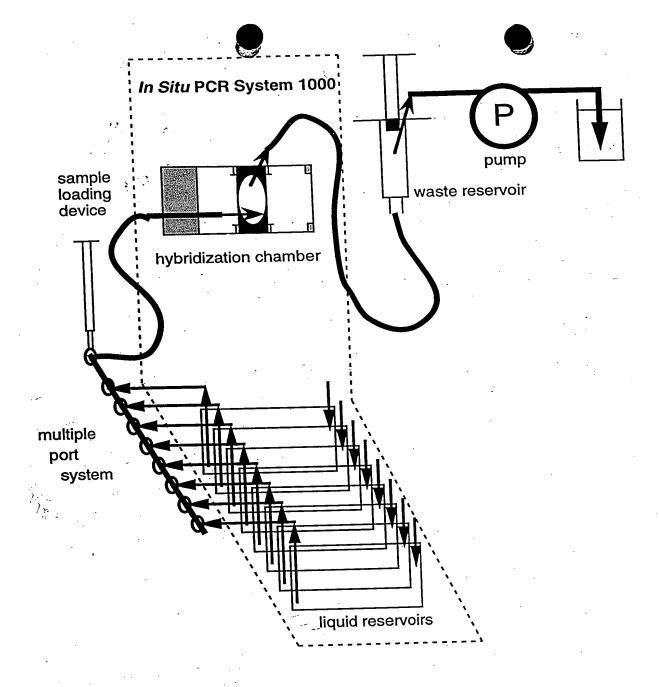


FIGURE 27

-COOH; probe 14
-NH2; probe 12
-NH2; probe 14

FIGURE 28

2% EGDMA

2% HDDMA

4% EGDMA

1 2

FIGURE 30

FIGURE 31

O

$$H_2C = C - C - (OCH_2CH_2)_n - OH$$

 CH_3 $n \sim 5$

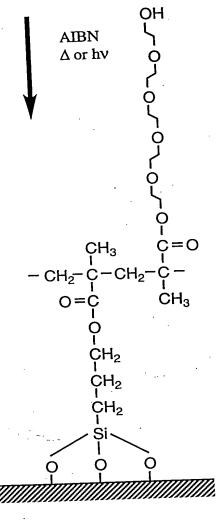
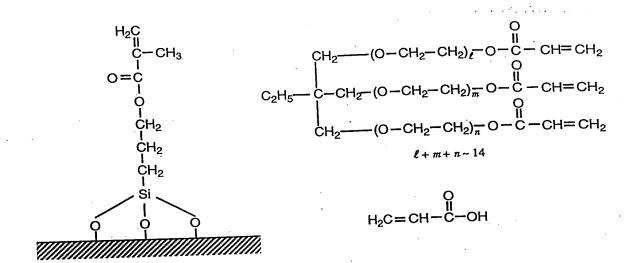


FIGURE 32



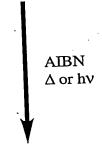




FIGURE 33

